

Primary Carcinoma of the Gallbladder in Taiwan

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To define more precisely the prognostic index for patients with primary carcinoma of the gallbladder in Taiwan, we retrospectively reviewed the data of 74 patients with gallbladder carcinoma treated over a period of 15 years, from 1979 to 1993. Of these patients, 75% had Nevin stage V gallbladder cancer. The most common presenting complaint was abdominal pain, followed by jaundice, fever, and nausea and vomiting. Accurate preoperative diagnosis was made in 29.7% of the patients. Ultrasonography and computed tomography had a diagnostic accuracy of 34.0% and 40.9%, respectively. The most common histologic type was adenocarcinoma. Liver was the organ most commonly invaded (51.9%) by direct extension and/or metastases, followed by regional lymph nodes (38.5%). The overall 5-year survival rate was 4.1%. Age, sex, white cell count, hemoglobin, SGOT, SGPT, total bilirubin, alkaline phosphatase, and cholelithiasis were not significant prognostic factors. Patients with cancers confined in the gallbladder wall (stages I, II, III) had a better ($P < 0.05$) cumulative survival rate than did those with regional lymph nodes and distant metastases. Cholecystectomy or extended surgery had a better survival rate than did palliative surgery, but there was no significant difference between cholecystectomy and extended surgery. High index of suspicion of the disease and earlier surgical treatment may improve patient survival. © 1996 Wiley-Liss, Inc.

KEY WORDS: cholecystectomy, cholelithiasis, gallbladder carcinoma, ultrasonography

INTRODUCTION

Although primary carcinoma of the gallbladder is relatively rare, it is the most common malignancy of the biliary system and the fifth most common gastrointestinal cancer diagnosed in the United States [1]. Despite improvements in diagnostic and therapeutic facilities, gallbladder carcinoma patients continue to have an extremely poor prognosis. In the majority of instances the lesions are considered unresectable at the time of surgical exploration [1–4]. Therefore, early detection with timely surgical resection is necessary to improve the survival rate in these patients. However, results of surgical treatment are controversial [5–9]. Little information is known about the patients with primary gallbladder carcinoma in Taiwan. It has been shown that there are pitfalls of applying the results of published studies to another population

[10,11]. To define this disease entity more precisely and to determine a prognostic index for gallbladder carcinoma patients, we retrospectively reviewed the data of 74 patients with primary carcinoma of the gallbladder treated between 1979 and 1993.

MATERIALS AND METHODS

During a period of 15 years from 1979 to 1993, 86 patients were diagnosed as having primary carcinoma of the gallbladder and treated at the Chang Gung Memorial Hospital, which is a university facility with 120 beds available to the patients of the Division of General Surgery. The medical records of 12 patients did not contain

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TABLE I. Clinical Features in 74 Patients With Gallbladder Carcinoma

Symptoms/signs	No. of patients (%)
Abdominal pain	60 (81.1)
RUQ pain	34 (50.0)
Epigastralgia	26 (35.1)
Jaundice	24 (32.4)
Fever	12 (16.2)
Nausea and vomiting	12 (16.2)
Flatulence	8 (10.8)
Malaise	4 (5.4)
Anorexia	3 (4.1)
Hepatomegaly	2 (2.7)
Abdominal mass	2 (2.7)
Abdominal distension	1 (1.4)
Weight loss	1 (1.4)
Constipation	1 (1.4)

TABLE II. Laboratory Data of Patients With Primary Gallbladder Carcinoma

	Mean \pm SE	Range
Hemoglobin (gm/dL)	11.4 \pm 0.2	4.5–15.7
Hematocrit (%)	33.6 \pm 0.7	13.7–45.6
WBC (/mm ³)	10,249 \pm 658	2,100–32,700
SGOT (U/L)	100.7 \pm 18.9	12–1,036
SGPT (U/L)	111.4 \pm 20.8	6–620
Alkaline phosphatase (U/L)	435.0 \pm 203.1	52–1,310
Bilirubin (mg%)		
Direct	4.0 \pm 0.8	0.2–19.9
Indirect	5.0 \pm 0.9	0.3–32.7

TABLE III. Diagnostic Accuracy With Various Imaging Methods

	Total	Correct (%)
Abdominal CT ^a	22	9 (40.9)
Ultrasonography	53	18 (34.0)
ERCP ^b	25	3 (12.0)
PTC ^c	11	1 (9.1)

^aComputed tomography.^bEndoscopic retrograde cholangiopancreatography.^cPercutaneous transhepatic cholangiography.

sufficient information and those patients were excluded from this report. The series consists of the remaining 74 patients who were treated, and the data concerning these patients were reviewed retrospectively. The patients were grouped according to the staging system of Nevin et al. [3]. The five stages were classified as follows: stage I, intramucosal tumor involvement only (2 patients, 2.7%); stage II, involvement of mucosa and muscularis (5 patients, 6.8%); stage III, involvement of all gallbladder wall layers including mucosa, muscularis, and serosa (14 patients, 18.9%); stage IV, involvement of all three layers and cystic duct lymph node (1 patient, 1.4%); stage

TABLE IV. Metastatic Sites in 52 Patients With Gallbladder Carcinoma

Metastatic sites	No. of patients (%)
Liver	27 (50.9)
Regional lymph nodes	20 (37.7)
Choledochal	11 (20.8)
Peripancreatic	5 (9.4)
Porta hepatis	3 (5.7)
Supraduodenal	1 (1.9)
Cystic	1 (1.9)
Distant lymph nodes	5 (9.4)
Mesenteric	3 (5.7)
Periaortic	2 (3.8)
Omentum	8 (15.1)
Hepatoduodenal ligament	8 (15.1)
Colon	6 (11.3)
Duodenum	6 (11.3)
Common bile duct	5 (9.4)
Abdominal carcinomatosis	4 (7.6)
Mesocolon	3 (5.7)
Peritoneum	2 (3.8)
Ovary	2 (3.8)
Common hepatic duct	2 (3.8)
Stomach	1 (1.9)
Pancreas	1 (1.9)
Uterus	1 (1.9)
Salpax	1 (1.9)

V, involvement of liver by direct extension or distant metastasis (52 patients; 70.3%). Extended surgery was defined as cholecystectomy with one or more of the following procedures: liver resection (partial hepatectomy or resection of gallbladder fossa), lymph node dissection along the hepatoduodenal ligament, resection of extrahepatic bile duct. Palliative surgery included cholecystostomy, tube drainage of the bile duct, or biopsy of the tumor only. Cholecystectomy was defined as cholecystectomy alone or cholecystectomy with drainage of the bile duct.

Data were presented as mean \pm standard error (SE). Cumulative survival rates of the patients were obtained by use of the Kaplan-Meier method and compared by use of the log-rank test. Statistical significance was defined as a *P* value < 0.05 .

RESULTS

Forty-five patients were female and twenty-nine were male (1.6:1). The age ranged from 35 to 91 years (65.4 ± 1.5 years) and the majority were in the sixth to eighth decades. The disease occurred at a slightly younger age in females (64.5 ± 2.1 years) than in males (66.8 ± 1.9 years).

As shown in Table I, the most frequent presenting complaints were abdominal pain, followed by jaundice, fever, and nausea and vomiting. Duration of symptoms prior to admission ranged from 1 day to 10 years (210.1 ± 84.2 days). The patients with earlier stage gall-

TABLE V. Operative Procedures in 74 Patients With Gallbladder Carcinoma

Procedures	Stages				
	I	II	III	IV	V
Cholecystectomy	1	1	9	1	4
Cholecystectomy, and wedge resection of liver	1				2
wedge resection of liver, resection of CBD, LN dissection					2
wedge resection of liver, right hemicolectomy					1
right lobectomy, right hemicolectomy					1
Cholecystectomy, choledochotomy		1	4		9
Cholecystectomy, choledochotomy, and wedge resection of liver					5
wedge resection of liver, LN dissection		1			1
wedge resection of liver, right hemicolectomy, subtotal gastrectomy					1
LN dissection		1			2
left hepatectomy		1			
Cholecystectomy, choledocholithotomy			1		2
Cholodochotomy					1
Cholecystostomy, biopsy					7
Cholecystostomy, biopsy, and choledocholithotomy					1
Exploratory laparotomy, biopsy					13
Subtotal	2	5	14	1	52

bladder cancers (stages I, II, and III) had significantly ($P < 0.05$, Mann-Whitney U test) longer duration of symptoms than did those with advanced (stages IV and V) cancers (524.0 ± 279.3 days vs. 84.6 ± 27.3 days). The interval between the onset of symptoms and hospitalization in the patients with coexistent cholelithiasis was significantly ($P < 0.05$, Mann-Whitney U test) different from those without cholelithiasis (149.9 ± 78.5 days vs. 290.4 ± 167.2 days). Abdominal pain was most frequently located at the right upper quadrant. Laboratory data are presented in Table II. There were no significant differences in laboratory data between stage I + II + III and stage IV + V groups. Forty-one patients (55.4%) had decreased levels of hemoglobulin (<12 gm/dL). Twenty (27.0%) patients exhibited leukocytosis ($>11,000/\text{mm}^3$). Twenty-nine patients (39.2%) had hyperbilirubinemia and 24 had clinical jaundice. Forty-two patients (56.8%) had elevated serum levels of alkaline phosphatase and 39 (52.7%) had elevated SGOT and SGPT levels. Hepatitis B antigen (HBsAg), alpha-fetoprotein (AFP), and carcinoembryonic antigen (CEA) were examined in 31, 26, and 19 patients, respectively.

HBsAg was positive in only six patients (19.4%). Serum levels of AFP and CEA were elevated in 2 (7.7%) and 8 (42.1%) patients, respectively.

Overall accurate preoperative diagnosis was made in 29.7% of the 74 patients with gallbladder carcinoma. Diagnostic accuracy of ultrasonography (US) and computed tomography (CT) was 34.0% and 40.9%, respectively (Table III). Among 18 patients accurately diagnosed by ultrasonography (US), 14 were stage V, one was stage III, and three were stage II. Similarly, eight stage V and one stage II patients were diagnosed accurately by CT before surgery. Liver scan (2 patients), upper gastrointestinal series (2 patients), celiac and superior mesenteric angiography (4 patients), percutaneous transhepatic cholangiography (PTC) (11 patients), and endoscopic retrograde cholangiopancreatography (ERCP) (22 patient) were not helpful in diagnosis. Gastric outlet obstruction was identified in a patient having upper gastrointestinal series.

Adenocarcinoma was the most common type of gallbladder cancer (85.1%), followed by carcinosarcoma (4.1%), squamous cell carcinoma (4.1%), adeno-

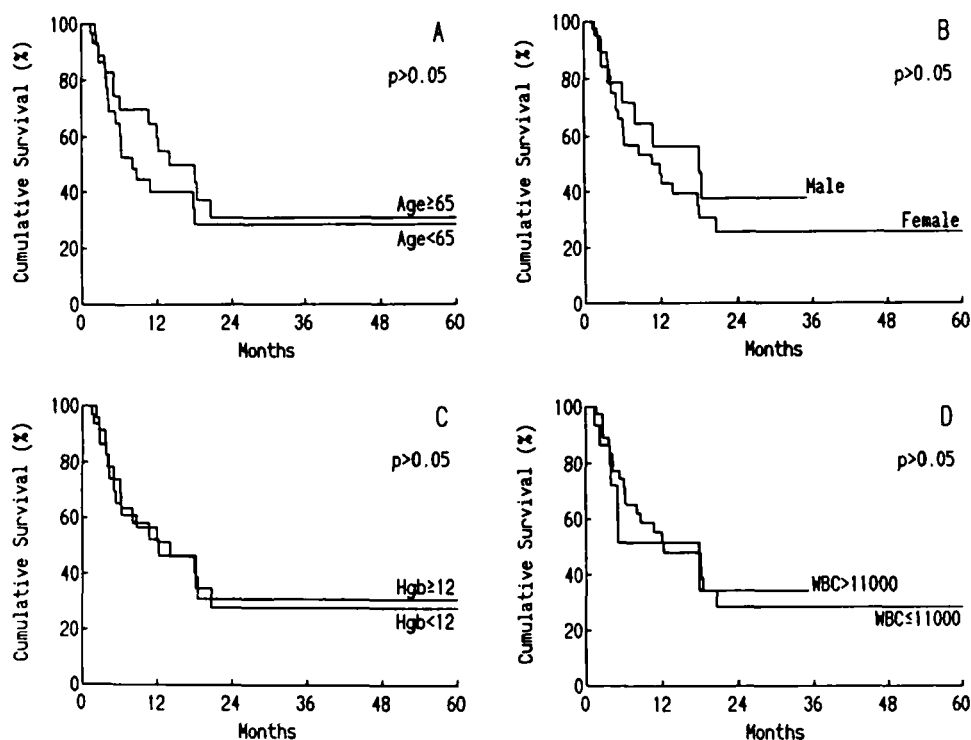


Fig. 1. Cumulative survival rates in the patients with gallbladder cancer. Factors affecting the survival rate were compared: (A) age, (B) sex, (C) hemoglobin, (D) WBC. The 30-day postoperative deaths are not included.

squamous carcinoma (4.1%), and anaplastic carcinoma (2.7%). One of the adenocarcinomas was found in a tubular adenoma of the gallbladder. Five were classified as papillary adenocarcinoma, four as mucinous carcinoma, and two as signet ring cell carcinoma. Fifty-two patients (70.3%) had either local invasion or distant metastases. Liver was the most commonly involved organ (51.9%) by local extension or metastases, followed by regional lymph nodes (38.5%), omentum (15.4%), and hepatoduodenal ligament (15.3%) (Table IV). Cholelithiasis were found in 46 patients (62.2%), of which 69.6% were gallbladder stones and 30.4% were choledocholithiasis.

The surgical procedures are shown in Table V. Extended procedures were performed in 18 patients (24.3%). Cholecystectomy was performed in 27 patients (36.5%). Seventeen patients (23.0%) were treated in a palliative fashion or for tissue diagnosis only. Cholecystectomy with or without wedge resection of liver was the main surgical procedure for stage I, II, and III tumors. In stage V patients, two were treated by cholecystectomy, resection of liver, and right hemicolectomy due to involvement of the right colon; two by cholecystectomy and resection of common bile duct (CBD). Of the stage V tumors, 71.2% were considered unresectable and were managed by palliative cholecystectomy, drainage procedures, or diagnostic tissue biopsy.

The 30-day postoperative mortality rate was 6.8%. The overall 1-year survival rate was 28.4%. Of the 21 patients who survived 1 year, two had stage I, four had stage II, five had stage III, and 10 patients had stage V diseases. The overall 5-year survival rate was only 4.1% (3/74), including one stage I, one stage III, and one stage V patient. The patients were grouped with various factors and the survivals between groups compared. Age, sex, white cell count, hemoglobin, SGOT, SGPT, total bilirubin, alkaline phosphatase, and cholelithiasis were not significant ($P > 0.05$) prognostic factor for survival (Figs. 1, 2). However, staging of gallbladder cancer is a significant ($P < 0.05$) prognostic factor (Fig. 3). The patients with cancers confined to the gallbladder wall (stages I, II, III) had a better survival rate than did those with tumors extending beyond the gallbladder wall (stages IV, V) (Fig. 3A). Stage II or stage III patients had a better survival rate than did stage V patients, but there was no difference in the survival between stage II and stage III patients. In addition, extended surgery or cholecystectomy had a better cumulative survival rate as compared to palliative procedures; however, the survival rate of extended surgery was not significantly ($P > 0.05$) different from that of cholecystectomy (Fig. 3B). In the patients with cancers confined to the gallbladder (stages I, II, III), extended surgery did not have a better survival than did cholecystectomy (Fig. 3C). In the patients with

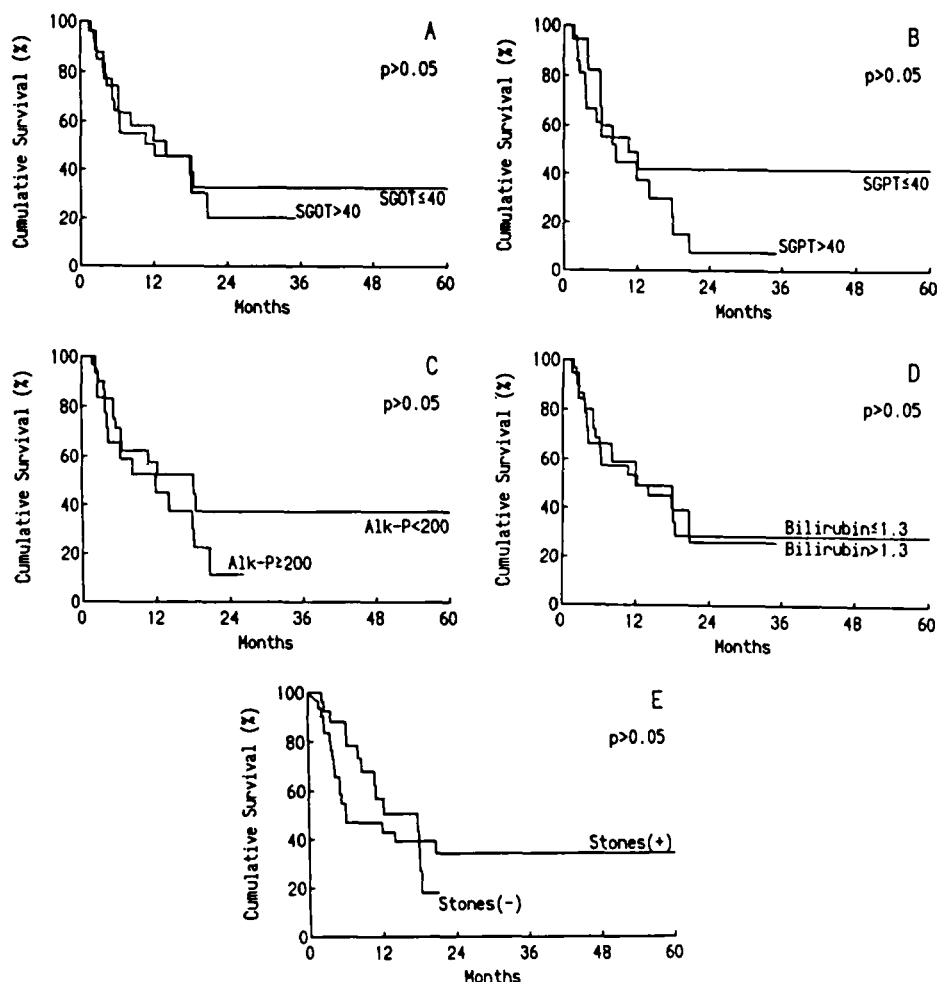


Fig. 2. Cumulative survival rates in the patients with gallbladder cancer. Factors influencing the survival rates were compared: (A) SGOT, (B) SGPT, (C) alkaline phosphatase (Alk-P), (D) bilirubin. The 30-day postoperative deaths are not included.

cancers beyond the gallbladder, cholecystectomy or extended surgery had a significant ($P < 0.05$) better survival than did palliative surgery (Fig. 3D), but there was no difference between cholecystectomy and extended surgery.

DISCUSSION

Surgical resection is the only current method of curing patients with gallbladder carcinoma, but 64–80% of the patients with gallbladder cancer are found to be unresectable at the time of operation [1,2,4]. In our series, the resectability rate was 32.8%. Surgical procedures for treating gallbladder carcinoma consist of cholecystectomy, cholecystectomy with resection of the gallbladder fossa and regional lymphadenectomy, and other more extensive procedures, such as hepatic lobectomy or pancreaticoduodenectomy [5,12]. Many investigators advocate cholecystectomy with wedge resection of the adjacent liver and regional lymphadenectomy for early cancer

confined in the gallbladder, because of frequent spread of gallbladder cancer to the adjacent liver and regional lymph nodes and poor prognosis of the disease [13–16]. However, Nevin et al. [3] recommended using a staging system to select the appropriate surgical method: stage I and stage II gallbladder cancers can be cured by simple cholecystectomy; stage III and stage IV tumors require radical procedures including liver resection and lymphadenectomy; stage V carcinomas are treated in a palliative fashion because of the extremely poor associated prognosis. In contrast, aggressive or radical procedures were reported to improve 5-year survival of advanced cases [5,6,12,17], but some reports did not show benefit from aggressive surgery [7–9]. In the present study, the survival rate of the patients treated with extended surgery was not better than that of the cholecystectomy group. These findings suggest that the extent of tumor invasion plays a more important role in the prognosis of gallbladder cancers.

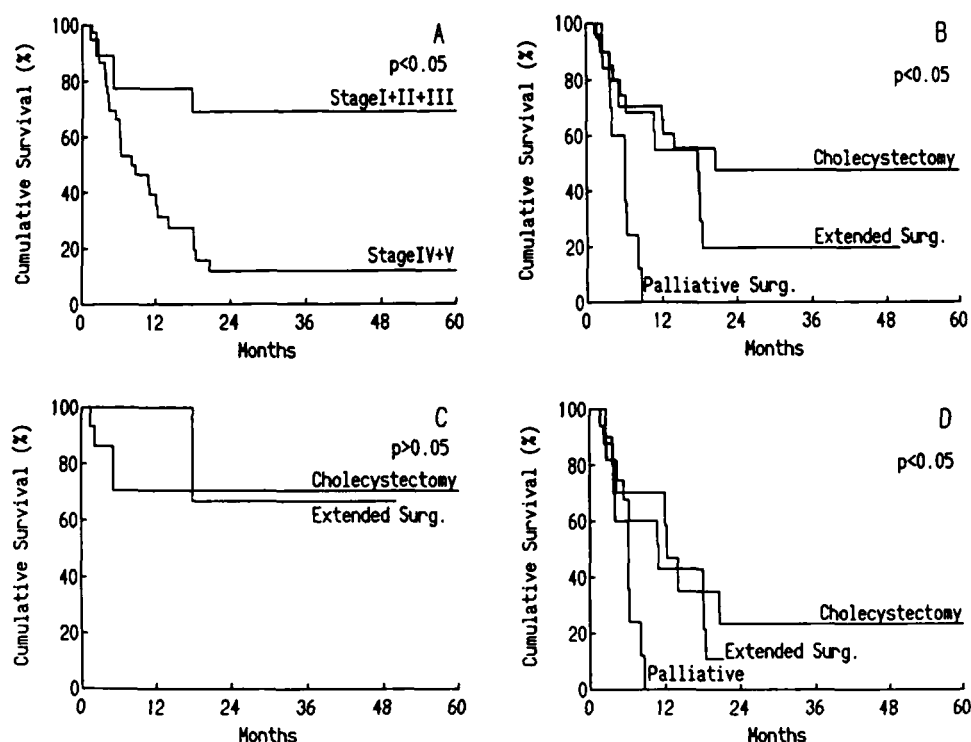


Fig. 3. Cumulative survival rates in the patients with gallbladder cancer. Factors influencing the survival rates were compared: (A) staging of gallbladder cancers, (B) operative methods, (C) operative methods for stage I + II + III cancers, (D) operative methods for stage IV + V cancers. The 30-day postoperative deaths are not included.

The overall prognosis of the gallbladder carcinoma is very poor, with an overall 5-year survival rate of $<5\%$ [15,18]. Overall, 5-year survival rate in the present study was 4.1% . The prognosis for the patients with carcinoma of the gallbladder is greatly influenced by the extent of invasion of the tumor into the gallbladder wall, lymph node involvement, and presence of distant metastases [19]. Similar to the results of other investigators, tumors confined to the gallbladder mucosa, muscularis, or subserosa (stages I, II, III) had a better prognosis than those extended beyond the serosa (stages IV, V) (Fig. 3). These findings suggest that early diagnosis of gallbladder carcinoma followed by appropriate therapy may improve the survival rate. However, the vague symptomatology of primary carcinoma of the gallbladder makes early diagnosis of this disease entity a challenge to the physician. The majority of gallbladder cancers are diagnosed late as shown in the present study that 70.3% of the patients were stage V disease. Patients often present with nonspecific symptoms that are indistinguishable from the benign biliary and gastrointestinal diseases [4,15,20]. Abdominal pain was the most frequent symptom in this group of patients, followed by jaundice, fever, nausea and vomiting (Table II). Laboratory tests, including liver function, AFP, HBsAg, and CEA, were not useful in the diagnosis of gallbladder carcinomas. In the present study, ERCP

and PTC did not aid in the diagnosis of gallbladder cancers. Recently, some investigators suggested US, CT, and magnetic resonance imaging (MRI) to detect gallbladder cancer [21–24]. However, as shown in the present study, although abdominal CT and US had a better diagnostic accuracy, 88.9% of CT-diagnosed and 77.8% of US-diagnosed cases were advanced gallbladder cancers.

In the past, some investigators have recommended prophylactic cholecystectomy to prevent the development of gallbladder cancer in patients with gallstones [4]. This approach was based upon the high incidence of gallstones in patients that developed gallbladder cancer [1,25]. However, this prophylactic modality has not been widely accepted by the surgical community. Carcinoma of the gallbladder occurs only in $\sim 1\text{--}2\%$ of patients with gallstones [1]. In a recent study, Lowenfels et al. [25] reported a very low risk of developing carcinoma of the gallbladder for middle-age white and black subjects of $<0.5\%$ over 20 years [25]. In another study done in Sweden, Broden and Bengtsson [26] reported that a marked decrease in the cholecystectomy rate did not affect the incidence of gallbladder cancer in a period of 8 years. Therefore, the indication of cholecystectomy should not be broadened with the specific intent of preventing gallbladder carcinoma.

CONCLUSIONS

The outcome of primary gallbladder carcinomas in Taiwan is similar to those reported in the literature. Carcinoma of the gallbladder remains a challenging disease entity that is difficult to diagnose and treat. Gallbladder cancers with earlier stages (stages I, II, III) and resectability have a better prognosis. These findings suggest that early detection of this disease is very important in improving the survival rate. Although ultrasonography or CT gives preoperative diagnostic accuracy, improved methods of early detection must be devised. Until such time, physicians must be alerted to the possibilities of this disease entity when faced with subtle symptomatology. Timely consideration to utilize available testing methods for diagnosis followed by appropriate therapy should be entertained.

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